UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,387	03/16/2004	Serge Auvin	427.062	5509

47888 7590 08/22/2006

HEDMAN & COSTIGAN P.C.
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,387	AUVIN ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *36* is/are allowed.

6)☒ Claim(s) *29-35 and 37-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/111,994.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-47 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I (drawn to compounds of formula I wherein A is A4 in which T is $-(CH_2)_m-$ wherein m is 1, i.e., indole compounds) in the reply filed on June 6, 2006 is acknowledged. The traversal is on the ground(s) that the restriction is improper. This is not found persuasive because the compounds of formula (I) are drawn to structurally dissimilar compounds, i.e., indole compounds (when m is 1) and quinoline compounds (when m is 2). Applicant's argument that 'the claims are drawn to a single inventive concept' is fully considered, however, the instant claims do encompass separate and distinct inventions that have acquired separate status in the art, will support separate patents, and will require different fields of search for the respective inventions. The instant claims are drawn to a plurality of compounds all of which are classified separately in various class/subclasses (involving review of thousands of patent documents) and require separate **burdensome** searches in the literature and computer databases. Compounds containing such diverse groups do not form a single inventive concept within the meaning of 35 U.S.C. 121 because a reference that anticipates or renders obvious one of the groups would not necessarily render obvious another group and applicants have not clearly stated on the record that this is not the case.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species of Example 36 is acknowledged. The species reads on claims 29-47. The species represents a compound of formula (I) wherein:

A is A4 wherein T is $-(CH_2)_m-$ wherein m is 1;

R^{38} is benzyl;

X is $-N(R^{45})-CO-NH-C(R^{46}R^{47})-CO-$ wherein R^{45} and R^{47} are H and R^{46} is i-butyl;

Y is $-(CH_2)_p-$ wherein p is 0; and

Het is 2-hydroxy-tetrahydrofuran-3-yl.

The guidelines in MPEP § 803.02 provide that upon examination if prior art is found for the elected species, the examination will be limited to the elected species.

Content of MPEP § 803.02 is provided here for convenience:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, **a second action on the merits on the elected claims would be final.**
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. **The prior art search, however, will not be extended unnecessarily to cover all nonelected species.** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species identically was not found in the prior art search and the search was expanded to the subgenus of formula (I) in wherein **A is A4** wherein **T is $-(CH_2)_m-$ wherein m is 1**; and **X is $-N(R^{45})-CO-NH-C(R^{46}R^{47})-CO-$ or $-(CH_2)_n-CO-$ wherein n is 0**; Y, Het, R^1, R^2, R^{38}, R^{45}, R^{46} and R^{47} as defined in the claims; and art was found. As per the guidelines of MPEP

§ 803.02, the Markush-type claims were examined to the extent of the searched subgenus. The generic subject matter (i.e., all other definitions of A and X) drawn to the non elected species from claims 29-35, 37-43 and 46-47 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a compound of formula (I) or a method of treating muscular dystrophy, does not reasonably provide enablement for a pharmaceutical composition for inhibition of calpains and/or reactive oxygen species generally; or a method of inhibiting calpain and/or reactive oxygen species in animals generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is

not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant composition claim 37 recites a particular intended use for the composition, i.e., 'for inhibition of calpains and/or reactive oxygen species', which according to the specification is directed to a wide list of therapeutic methods and the specification, does not provide enablement for all the listed disorders. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claims 38-47 are drawn to 'a method of inhibiting calpain and/or reactive oxygen species in warm-blooded animals'. The specification pages 52-53 provides pharmacological procedures to study the effects of the compounds, however, there is no test data or inhibition results provided for any the compounds of the instant claims. As the instant claim recites 'a method of inhibiting calpain and/or reactive oxygen species in warm-blooded animals', the claim is directed to 'a method of treating a disease mediated by the enzymes' and the specification provides an exhaustive list of diseases that are associated with the potential role of calpains and ROS's, see pages 1-2. The instant claims appear to be a 'reach through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays provided in the specification on pages 52-53 are related to inhibition of calpain I and the instant claims are drawn to 'a method of inhibiting calpain and/or reactive oxygen species in warm-blooded animals', however, there is neither data on how many compounds were tested nor data on which enzymes were inhibited and which ones were not. Applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification page 18, "the properties of the compound", which may be determined by the *in vitro* data holds significant role in determining the effective amount requirement for pharmaceutical dosage regimen to achieve the desired biological activity.

The specification provides a wide list of diverse disorders based on the inhibiting activity, see pages 1-2. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as calpain inhibitors and/or ROS traps, useful to treat a laundry list of diseases, which include inflammatory and immunological diseases, cardiovascular and cerebrovascular diseases, disorders of the central or peripheral nervous system, proliferative diseases, autoimmune and viral diseases, cancer, etc. Test assays and procedures are provided in the specification in pages 52-53 related to inhibition of calpain I and it was concluded that the compounds of the invention exhibit inhibitory activity, however, there is nothing in the disclosure regarding how this test data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of cancer, inflammatory diseases, CNS disorders, viral diseases, autoimmune diseases, etc., some of which have been proven to be extremely difficult to treat. Further, there is no

reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims recite treating of diseases mediated by calpains and/or reactive oxygen species, and there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms or inhibit calpain and/or reactive oxygen species generally. Further, there is no disclosure regarding how the patient in need of the treatment requiring the specific inhibiting activity is identified and further, how all types of the diseases having divers mechanisms are treated. The state of the art is indicative of the unpredictability of the therapeutic approach based on calpain and/or reactive oxygen species inhibiting activity. Wang et al. (PubMed Abstract 1994) indicate that "calpain could play a key or contributory role in the pathology of a variety of disorders, including cerebral ischemia, cataract, myocardial ischemia, muscular dystrophy and platelet aggregation. ..... At present, it is difficult to confirm the exact role of calpain in these disorders because of the lack of potent, selective and cell-permeable calpain inhibitors". A recent reference, Carragher (PubMed Abstract 2006) provides that "a major limitation to the clinical use of such inhibitors is their lack of specificity among cysteine proteases and other proteolytic enzymes". Regarding reactive

oxygen species, a state of the art reference Touyz (Hypertension 2004) states that "What remains unclear is (1) exactly how ROS regulate signaling molecules in the cardiovascular system, (2) what tips the balance to a prooxidant state in hypertension, ... Accordingly, the need to pursue research in the field of ROS, ... is more important than ever" (see page 251).

Enablement for the scope of "treating inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall

something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The specification provides 'treatment of cancer' as an example of beneficial effect of the potential role of calpain and/or reactive oxygen species inhibitors. A 'cancer' or 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No

compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity' effect of a 'disease' solely based on the inhibitory activity disclosed for the compounds.

It is inconceivable as to how the claimed single class of compounds can treat viral diseases generally. For example, there is no known common therapeutic mechanism for viral diseases generally. There are more than 400 distinct viruses that infect humans producing a wide range of diseases. The Merck Manual of Diagnosis and Therapy states that "Several hundred different viruses infect humans. Because many have been only recently recognized, their clinical effects are not fully understood" and "Only a few viral diseases can be diagnosed clinically or epidemiologically" see

<http://www.merck.com/mrkshared/mmanual/section13/chapter162/162a.jsp>. Cecil Textbook of Medicine states that "for many viral infections, no specific therapy exists. Proper use of antivirals requires specific viral diagnosis" (see the enclosed article, page 1742).

Further, the list of the diseases in the specification includes 'neurodegenerative diseases' which covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

'Cardiovascular and cerebrovascular diseases' embrace a vast array of problems, many of which are contradictory to others. For example, the term covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33 and 38-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 33, in the definition of D, the recitation "selected from the group consisting of" is redundant as only one term (phenylene) follows the recitation. Deletion is suggested.
2. In claim 38, the recitation "R_a^1 is hydrogen, -OR^3, -SR^3, oxo and cyclic acetal" is confusing because the recitation does not provide the groups recited for Ra1 in the alternative.
3. In claim 38, the definition provided for Y_a (see below) is confusing.

Y_a is selected from the group consisting of –$(CH_2$ -$(CH_2)_p$-;

Applicant's attention is directed to claim 29 wherein the analogous term Y in compound of formula (I) is provided as " –$(CH_2)_p$- ". Appropriate correction in claim 38 is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

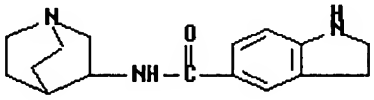
1. Claims 29, 32, 35, 37-38, 41, 44 and 46-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Kubo et al. (JP 2000-143635). The instantly claimed compounds read on reference disclosed compounds, see the structural formula (I) and the species in the corresponding CAPLUS Abstract 133:805. The reference discloses that the compounds have therapeutic effect on various diseases including inflammatory diseases, etc. (see the CAPLUS abstract). The instant claims 38, 41, 44, 46 and 47 read on the prior art taught therapeutic effect because the instant claims are drawn to administration of the prior art compounds, in same dosages, to the same patient population. The prior art also teaches that the compounds are useful in the treatment of the diseases which are same as those due to the beneficial effects recited in the instant claims and therefore, the instantly claimed mechanism of inhibition of calpain and/or reactive oxygen species is inherently taught in the reference.

Note: Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

2. Claims 29, 32, 35, 37-38, 41, 44 and 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Satoh et al. (CAPLUS Abstract 123:198771, 1995). The instantly claimed compounds read on reference disclosed compound, see the structural formula of compound having RN 167645-27-4 in the enclosed copy of CAPLUS database search report. The reference discloses that the compounds have therapeutic effect on various diseases including pancreatitis. (see the CAPLUS abstract). The instant claims 38, 41, 44, 46 and 47 read on the prior art taught therapeutic effect because the instant claims are drawn to administration of the prior art

compounds, in same dosages, to the same patient population. The prior art also teaches that the compounds are useful in the treatment of the diseases which are same as those due to the beneficial effects recited in the instant claims and therefore, the instantly claimed mechanism of inhibition of calpain and/or reactive oxygen species is inherently taught in the reference.

3. Claims 29, 32, 35, 37-38, 41, 44 and 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Azria et al. (GB 2193633). The instantly claimed compounds read on reference disclosed compound, see formula (I) in page 2 wherein A is a group of formula (IIa); B is –CO-; C is –NH-; and D is a heterocyclic group of formula (VI) to (IX) and the corresponding species of compound No. 127 in page 26 (The structural formula depicted below for convenience):



The reference discloses that the compounds have therapeutic effect on various diseases including ulcerative colitis, Crohn's disease, etc. (see page 15, lines 9-16). The instant claims 38, 41, 44, 46 and 47 read on the prior art taught therapeutic effect because the instant claims are drawn to administration of the prior art compounds, in same dosages, to the same patient population. The prior art also teaches that the compounds are useful in the treatment of the diseases which are same as those due to the beneficial effects recited in the instant claims and therefore, the instantly claimed mechanism of inhibition of calpain and/or reactive oxygen species is inherently taught in the reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-35, 37-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al., WO 97/48697. The reference teaches a generic group of azabicyclic compounds, which embraces applicant's instantly claimed compounds. See formula (I) in page 5, and the subgenus of formula (Ie) in page 50 wherein R^3 is $-C(=Z)-NR^6R^7$ wherein R^6 is optionally substituted heteroaryl wherein the substituents include halogen, alkyl, hydroxy, oxo, etc. The reference further discloses specific compound falling within the above subgenus, see the compound of Example (bh) in page 186, lines 1-2. The compounds are taught to be useful as pharmaceutical therapeutic agents for the treatment of diseases such as inflammatory diseases, etc., see pages 68-69. The instant claims differ from the reference by reciting a subgenus that overlaps with the reference taught compounds. It would have been obvious to one having

ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. (Note: The prior art also teaches that the compounds are useful in the treatment of the diseases which are same as those due to the beneficial effects recited in the instant claims and therefore, the instantly claimed mechanism of inhibition of calpain and/or reactive oxygen species is inherently taught in the reference). One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Allowable Subject Matter

Claim 36 is allowed. The references of record do not teach or fairly suggest the instantly claimed compounds.

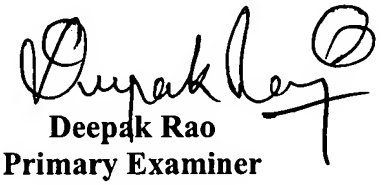
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

August 18, 2006